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ORIGINAL ARTICLE

Mortality in type 1 diabetes diagnosed in childhood in Northern Ireland during 1989-2012: A population-based cohort study

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Objective: To investigate long-term mortality rates and causes of death in individuals diagnosed with type 1 diabetes before the age of 15 years during the period 1989-2012 or known to paediatric diabetes teams in 1989, in Northern Ireland.

Methods: A cohort of 3129 patients from the Northern Ireland Childhood Diabetes Register was linked to death registrations and underlying causes, coded according to ICD-9 or ICD-10. Standardized mortality ratios (SMRs) were calculated as the ratio of observed to expected deaths by sex, attained age, time since diagnosis, calendar period, and cause of death.

Results: Subjects were followed to December 31, 2012 giving 39 764 person-years of follow-up (median 12.1 years). In total, 59 subjects had died (1.5 per 1000 person-years) compared with 19.9 deaths expected, an SMR of 296 (95% confidence interval (CI) 229-382). Women had a significantly higher excess risk of mortality than men with SMRs of 535 (95% CI 361-764) and 203 (95% CI 136-291), respectively. Over half of the deaths (56%) were judged to be related or possibly related to diabetes with most of these due to acute ($n = 24$) or late ($n = 6$) complications.

Conclusions: Subjects with type 1 diabetes diagnosed less than 15 years of age had 3 times the mortality risk of the general population. Over half of the deaths were related to acute or chronic complications of diabetes.

KEYWORDS

mortality, standardized mortality ratio, type 1 diabetes

1 | INTRODUCTION

Despite advances in treatment and management, an excess mortality in people diagnosed with type 1 diabetes compared to the general population persists. Most excess mortality in young people with type 1 diabetes has been attributed to acute diabetes-related complications, mainly diabetic ketoacidosis (DKA) and, to a lesser extent, hypoglycaemia.¹ As both of these complications are largely preventable through education and improved glycaemic control, as well as increased awareness, one might anticipate a decline in such deaths in recent years.

Other causes of excess mortality that have been reported in older patients with diabetes include renal disease and cardiovascular

disease (CVD), both late complications of diabetes.¹ In addition, a high number of drug-related deaths among type 1 diabetes subjects compared to the general population has been reported.² With previous reports that the incidence of type 1 diabetes is increasing both in Europe³ and worldwide,⁴ it is important that mortality in these individuals is monitored to determine if current treatments for type 1 diabetes are effective in reducing excess deaths.

A number of population-based studies investigating mortality in patients with type 1 diabetes diagnosed in childhood and adolescence have been published in recent years but most have relatively short follow-up after diagnosis.⁵ Larger studies with longer follow-up permit investigation of trends in mortality rates over time. In this

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study, we aim to investigate mortality in type 1 diabetes diagnosed in childhood in Northern Ireland.

2 | PATIENTS AND METHODS

A cohort of subjects diagnosed with type 1 diabetes in Northern Ireland was extracted from the Northern Ireland Childhood Diabetes Register. The cohort consists of 2502 incident cases diagnosed with type 1 diabetes between January 1989 and December 2012 and who were prospectively added to the register. A further 627 prevalent cases, diagnosed with type 1 diabetes under the age of 15 years prior to 1989 that were known to paediatric diabetes teams at the time the register was established, were also included.

Information on deaths was obtained through linkage to the National Health Service patient database maintained by the Northern Ireland Business Services Organisation using Health and Care number as a unique identifier. Further information about the causes and circumstances of deaths were obtained from the Registrar General's Office, from postmortem reports obtained from the State Pathologist's Office and from any other available sources (eg, press reports).

Underlying causes of deaths were as coded by staff of the Registrar General's Office using International Classification of Diseases (ICD) revisions 9 (1989-2000) and 10 (2001-2012). One clinician, CRB, reviewed the available information on all deaths and assigned deaths to one of the following 6 categories: (1) DKA, (2) hypoglycaemia, (3) other/uncertain acute complication of diabetes, (4) late complication of diabetes, (5) possibly related to diabetes, and (6) unrelated to diabetes. Deaths in categories (1) to (4) were regarded as being definitely due to diabetes. Where sufficient information was available, deaths with an underlying cause coded as diabetes were reassigned to another cause mentioned on the death certificate (eg, coronary heart disease or chronic renal failure). A second clinician experienced in adult diabetes care, DRM, reviewed all deaths for which there was doubt about the assignment and approved all cause reassignments.

The Northern Ireland Childhood Diabetes Register (reference 07/NIR02/78) and the mortality follow-up (reference 13/NIR03/52) were approved by the Office for Research Ethics Committees Northern Ireland. Since 2007 consent has been sought for a child to be included in the register.

3 | STATISTICAL ANALYSES

Prospective and retrospective cases were followed up from their date of diagnosis or from January 1989, respectively. Subjects were followed until the earliest of their date of death, emigration or the end of the study on December 31, 2012. The person-years at risk method⁶ was used to compare the observed number of deaths in the register cohort with the number of deaths expected were the cohort to have experienced Northern Ireland mortality rates specific for each combination of sex, 5-year period, and 5-year age-group, as published by the Northern Ireland Registrar General's Office (<http://www.nisra.gov.uk/demography/default.asp.htm>). Standardized mortality ratios (SMRs) were calculated as the ratio of total observed to total

expected deaths and absolute mortality rates per 1000 person-years were also calculated. The 95% confidence intervals (CIs) for SMRs and absolute rates were derived from exact 95% CIs for Poisson distribution counts and ratios of 2 SMRs with 95% CIs were also calculated.⁷

Mortality was reported by sex, cohort subgroup (retrospective or prospective), attained age, time since diagnosis, and calendar period. Poisson regression likelihood ratio tests were used to investigate if SMRs differed significantly between subgroups. Cause-specific SMRs were also calculated.

4 | RESULTS

There were 48 cases (20 prospective and 28 retrospective) that could not be linked, for 21 of which (5 prospective and 16 retrospective) no Health and Care number could be found. All were excluded from the analysis as were 2 patients for whom consent was withheld. Three deaths occurring at the time of diagnosis were also excluded from all analyses. In total, 3129 cases of childhood type 1 diabetes were included in the analysis providing 39 764 person-years of follow-up (median follow-up, 12.1 years, interquartile range 5.9-20.1 years). There were slightly more males than females (51%). Of these patients, 2502 were prospectively added to the register from 1989 onwards while the remaining 627 patients were added retrospectively. In total, 246 (8%) subjects were lost to follow-up at the time of their move to another part of the UK or their emigration to another country.

5 | ALL CAUSE-MORTALITY

Overall, there were 59 deaths during the study follow-up (1.5 deaths per 1000 person-years). Results from the person-years at risk analysis are shown in Table 1. The 59 deaths in the cohort compared to 19.9 deaths expected from the background population rates gave an overall SMR of 296 (95% CI 226-382). The SMR in females was significantly higher ($\chi^2 = 13.43$, $df = 1$, $P < .001$) at 534 (95% CI 360-762) compared to males with an SMR of 202 (95% CI 136-291). The ratio of these 2 SMRs was 0.38 (95% CI 0.22-0.65). However, there was no significant difference in absolute mortality between the 2 sexes ($\chi^2 = 0.03$, $df = 1$, $P = .85$). Similar excesses in deaths were observed in the prospective and retrospective cohort subgroups with SMRs of 282 (95% CI 191-403) and 312 (95% CI 209-448), respectively. Excess mortality did not appear to be associated with attained age, time since diagnosis, or calendar period. Absolute mortality rates increased with age and duration of type 1 diabetes.

6 | CAUSE-SPECIFIC MORTALITY

Diabetes was mentioned on 42 of the 59 death certificates (71%). Over half of the deaths (56%) were judged to be related to diabetes or possibly related to diabetes. The majority of diabetes-related deaths were due to acute complications ($n = 24$ [41%]). DKA was the

TABLE 1 Results of mortality follow-up in Northern Ireland Childhood Diabetes Register during 1989-2012

Subgroup	Person-years of follow-up	Observed (expected) deaths	Mortality rate per 1000 person-years	SMR (95% CI)	P (P for trend) ^a
Total	39 764	59 (19.9)	1.5	296 (226, 382)	
Sex					
Males	20 026	29 (14.3)	1.5	202 (136, 291)	<.001
Females	19 739	30 (5.6)	1.5	534 (360, 762)	
Cohort subgroup					
Prospective	26 363	30 (10.6)	1.1	282 (191, 403)	.71
Retrospective	13 401	29 (9.3)	2.2	312 (209, 448)	
Attained age					
0-14 y	14 086	10 (2.3)	0.7	443 (212, 815)	.07 (.73)
15-19 y	9325	10 (4.9)	1.1	204 (98, 376)	
20-24 y	6907	9 (4.7)	1.3	190 (87, 361)	
25-29 y	4585	17 (3.2)	3.7	540 (314, 864)	
30-34 y	2755	6 (2.1)	2.2	285 (104, 620)	
35+ y	2106	7 (2.8)	3.3	252 (101, 519)	
Time since diagnosis					
0-4 y	11 719	8 (2.8)	0.7	285 (123, 561)	.92 (.95)
5-9 y	9629	12 (3.9)	1.2	306 (158, 535)	
10-14 y	7273	11 (4.1)	1.5	266 (133, 476)	
15-19 y	5111	12 (3.4)	2.4	351 (181, 612)	
20+ y	6032	16 (5.7)	2.7	283 (162, 460)	
Calendar period					
1989-1993	4016	9 (1.6)	2.2	548 (250, 1040)	.10 (.31)
1994-1998	5915	10 (2.6)	1.7	390 (187, 717)	
1999-2003	8286	7 (3.8)	0.9	184 (74, 378)	
2004-2008	10 949	12 (5.9)	1.1	205 (106, 357)	
2009-2012	10 598	21 (6.1)	2.0	347 (215, 530)	

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

^a P-values from Poisson regression likelihood ratio tests to investigate if SMRs differed between subgroups.

most common acute complication ($n = 15$) and 8 deaths were due to hypoglycaemia. Another death was categorized as an uncertain acute complication because the postmortem report was inconclusive. Only 6 deaths (10%) were related to late complications of diabetes, a reflection of the relatively young age of the cohort. Three of the deaths were deemed possibly related to diabetes although the exact role played by diabetes could not be determined due to uncertainties about the cause of death. There were 26 ($n = 44\%$) deaths that were classified as unrelated to diabetes.

Eight of the 30 deaths with diabetes coded as the underlying cause could be reassigned to another cause mentioned on the death certificate (4 due as CVD, 2 as accident and violence including suicide, and 2 as chronic renal disease).

Mean age at death was similar across each cause of death, diabetes (22.7 years), accidents and violence (23.3 years), cancer (25.2 years), drug misuse (25.0 years), and other (23.4 years), except CVD (36.5 years). Figure 1 shows the observed and expected deaths by cause of death. There was no significant excess in deaths due to cancer, accident or violence (including suicide), or CVD.

Alcohol was mentioned in 7 (12%) of the death certificates or postmortems. Although drug misuse had been reported in 4 (7%) of the death certificates or postmortems, only 1 death from unintentional poisoning was registered as the underlying cause and could

therefore contribute to the SMR calculation. This resulted in little evidence of an excess of drug-related deaths (SMR = 76, 95% CI 2-424).

7 | DISCUSSION

The primary aim of this follow-up study was to investigate mortality in subjects diagnosed with type 1 diabetes before the age of 15 years in Northern Ireland. During an extensive 24 years of follow-up, there was a 3-fold excess in mortality in patients with type 1 diabetes compared to the general population (SMR 296, 95% CI 229-382). Significant excess was observed in both prospective and retrospective groups and in each time since diagnosis category.

Our recent systematic review of mortality in young people diagnosed with type 1 diabetes showed that, while some of the studies reported similar excess in deaths, other studies in the review showed a much higher excess of deaths.⁸ These latter findings were usually associated with older studies and studies in countries with higher infant mortality rates and lower health expenditures.⁸ More recently published studies⁹⁻¹² have also shown higher excess mortality in young people with type 1 diabetes compared to our own study, but these studies pertained to patients with an earlier calendar period of diagnosis.

Despite finding that females had a significantly higher risk of mortality than males compared to the general population (SMR = 534

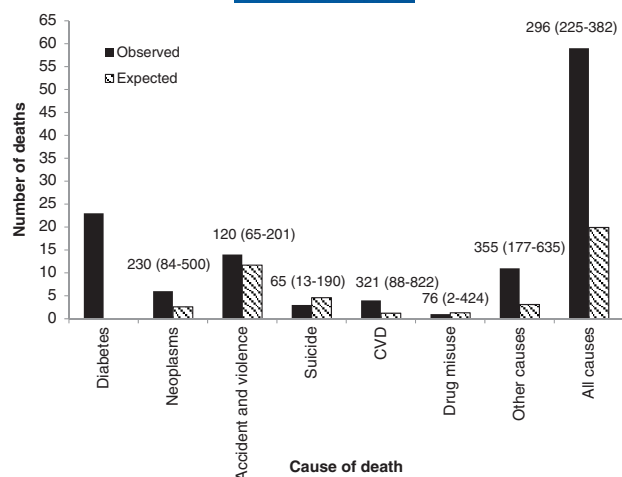


FIGURE 1 Observed and expected deaths by cause of death for deaths (with standardized mortality ratio [SMR] and 95% confidence interval [CI]) occurring in the Northern Ireland Childhood Diabetes Register, 1989-2012. Deaths by accident and violence include suicide. Deaths coded with diabetes as the underlying cause were reclassified to another cause that was mentioned on the death certificate. ICD-10 (ICD-9) codes: Diabetes, E10-E14 (250); neoplasms, C00-C97, D00-D48 (140-239); accident and violence (including suicide), V00-Y98 (E800-E999); suicide, X60-X84 (E950-E959); cardiovascular disease (CVD), I00-I99 (390-459); drug misuse, F11-F16, F18-F19, X40-X44, X60-X64, Y10-Y14, X85 (292, 304, 305.2-305.9, E850-E858, E950.0-E950.5, E980.0-E980.5, E962.0); other causes, all remaining ICD codes

vs 202), absolute mortality rates were similar (1.5 per 1000 person-years in both sexes). Such higher excesses relative to the lower background population death rates in females has been observed in other studies,^{5,13-15} although the absolute numbers of excess deaths in each sex were similar. This finding is an indication that the low mortality experienced in females in the background population is not mirrored in women with type 1 diabetes, as absolute mortality rates were similar in the 2 sexes.

We found that the risk of death was significantly higher in both prospective and retrospective groups compared to the general population (SMRs = 282 and 312, respectively). As expected, most deaths due to late complications of diabetes, including CVD and chronic renal failure, occurred in the retrospective group. Subjects in this group were generally older than the prospective cases and had a longer duration of diabetes with diagnosis occurring prior to 1989. However, 1 patient in the prospective cohort died from end-stage renal disease after 21 years of diabetes, highlighting that deaths due to chronic complications of diabetes can occur at younger ages. Given the fact that the cohort under study had a maximum follow-up of 24 years, and that only 5% of follow-up occurred beyond the age of 35 years, it is not surprising that few deaths due to late complications occurred.

Many diabetes-related deaths are now preventable through achieving optimum glycated haemoglobin (HbA1c) levels. Sandahl et al⁹ identified baseline HbA1c as a significant predictor of mortality with a 38% increase in risk of death for every 1% increase in HbA1c. With the implementation of intensive education programmes and insulin regimens in recent years, one might anticipate a decrease in the rates of both DKA and severe hypoglycaemia. Thus, it is of major

concern that almost a quarter (24%) of deaths were due to potentially preventable acute complications of type 1 diabetes. A previous audit of diabetes care provision and glycaemic control in Northern Ireland¹⁶ found that mean HbA1c was 8.8% (73 mmol/mol) in 2002 with only 20% of children achieving target levels of less than 7.5% (58 mmol/mol). It would be expected that if intensive diabetes treatment regimens, and the uptake of insulin pumps in conjunction with education programmes¹⁷ were to increase in the United Kingdom in line with other countries,¹⁸ there would be improvements in HbA1c^{19,20} and reductions in subsequent diabetes-related complications²¹ and mortality.

High proportions of deaths due to acute complications have been reported in similar studies.² This study and other similar studies highlight that the excess deaths in diabetes patients is largely due to preventable acute complications and there is a need to identify those patients who are at risk of such complications. The British Diabetes Association mortality study²² investigated psychosocial and socioeconomic risk factors of acute deaths in type 1 diabetes patients diagnosed under the age of 30 years in the United Kingdom. The authors found that living alone (odds ratio [OR] = 4.4), past drug misuse (OR = 5.7), and previous psychiatric referral (OR = 4.6) were significantly associated with death from acute complications.

There was little evidence of an excess of drug-related deaths (including insulin but excluding alcohol and tobacco) in this study but the numbers were too small for any definitive conclusion. Excess deaths related to drug misuse in type 1 diabetes patients have previously been reported by Feltbower et al² with 6 of the 17 drug-related fatalities they observed being due to insulin overdoses. In our study, only 1 death from the suicide was due to insulin overdose. However, a high proportion (12%) of deaths in Northern Ireland was felt to have been related to alcohol in death certificates or postmortem reports. A study by Webb et al²³ investigating the risk of unnatural deaths in individuals with diabetes (type 1 or type 2) reported a 3- to 5-fold increase in risk of deaths related to alcohol and drug misuse. Another study investigating mortality in individuals with type 1 diabetes found a high proportion (25%) of alcohol and drug-related deaths in patients diagnosed before 15 years of age at 20 years duration of diabetes.¹⁵ In this study, we found that drug or alcohol use was mentioned in 15% of the death certificates or postmortem reports in Northern Ireland. It is difficult to know the exact role of alcohol and drug misuse in these patients' deaths. Alcohol consumption is known to increase the risk of an immediate and prolonged hypoglycaemia²⁴ but it may not necessarily be mentioned in the registered causes of death. This may be particularly pertinent to Northern Ireland due to the high level of alcohol consumption among young people.^{25,26} We speculate that some young patients living with this long-term condition, unaware of the hazards of alcohol excess, may abuse alcohol potentially placing their safety and well-being at risk. It is important that education and support is provided for patients to raise awareness of the risk of alcohol consumption and the effect it can have on metabolic control.

A major strength of this study is that it is unlikely that any deaths would have been missed as might have occurred if only death certificates mentioning diabetes had been used to ascertain mortality.²⁷ Furthermore, the availability of death certificates and autopsy reports

provided detailed information on the 59 deaths to allow accurate assignment and categorization of cause of death.

One limitation of this study is that 246 subjects who were lost to follow-up and this 8% of the cohort were consequently censored at their date of emigration from Northern Ireland. The absolute mortality in this cohort may consequently be underestimated as a higher proportion of subjects who emigrated were in the older retrospective subgroup, but our person-years approach to analysis takes age into account so our SMRs should not be affected as much by this source of bias. Lastly, despite the availability of death certificates and autopsy reports, it was still not possible to determine whether some deaths were directly attributed to diabetes due to difficulty in interpreting glucose levels postmortem.²⁸

In conclusion, our data show that there is still a significant excess in mortality in type 1 diabetes patients in Northern Ireland. With a high proportion of deaths due to DKA or hypoglycaemia, continuing efforts should be made to raise awareness and educate patients in order to improve blood glucose control and reduce the risk of death due to these preventable complications.

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Conflict of interest

All authors declare that there is no duality of interest associated with this manuscript.

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